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Original Article

Adaptive servo-ventilation as treatment of persistent central sleep apnea in post-acute ischemic stroke patients

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ABSTRACT

Background: Adaptive servo-ventilation (ASV) is a well-established treatment of central sleep apnea (CSA) related to congestive heart failure (CHF). Few studies have evaluated the effectiveness and adherence in patients with CSA of other etiologies, and even less is known about treatment of CSA in patients of post ischemic stroke.
Methods: A single-centre retrospective analysis of ASV treatment for CSA in post-acute ischemic stroke patients without concomitant CHF was performed. Demographics, clinical data, sleep studies, ventilator settings, and adherence data were evaluated.
Results: Out of 154 patients on ASV, 15 patients had CSA related to ischemic stroke and were started on ASV a median of 11 months after the acute cerebrovascular event. Thirteen out of the 15 patients were initially treated with continuous positive airway pressure (11/15) and bilevel positive airway pressure (2/15) therapy with unsatisfactory control of CSA. ASV significantly improved AHI (46.7 ± 24.3 vs 8.5 ± 12/h, $P = 0.001$) and reduced ESS (8.7 ± 5.7 vs 5.6 ± 2.5, $P = 0.08$) with a mean nightly use of ASV of 5.4 ± 2.4 h at 3 months after the initiation of treatment. Results were maintained at 6 months.
Conclusion: ASV was well tolerated and clinically effective in this group of patients with persistent CSA after ischemic stroke.

1. Introduction

Sleep disordered breathing (SDB) is common after ischemic stroke and can be found in about 50–70% of patients [1,2]. SDB improves over time in many cases, but about 50% of stroke patients continue to have an elevated apnea–hypopnea index (AHI) of ≥10/h 3 months after the acute event [1,3–5]. Central apneas and Cheyne Stokes Respiration (CSR) tend to improve better than obstructive apneas, but nevertheless persist in 6–29% of stable stroke patients [2–4,6,7]. Central sleep apnea (CSA) is a negative prognostic factor in acute stroke [8,9] and related to stroke severity and topography and often, but not necessarily, to left ventricular (LV) systolic dysfunction [7,8,10–12]. The evidence on the detrimental effect of SDB in stroke patients and the benefits of treating obstructive sleep apnea (OSA) with continuous positive airway pressure (CPAP) in this population is constantly growing [1,3,13–17], but data supporting the treatment of CSA in the immediate or post-acute stroke period is still scarce. Nevertheless, treatment of persistent CSA in stroke patients is considered in clinical practice, particularly if a high AHI, excessive daytime sleepiness (EDS) or other symptoms are present [18]. CPAP can occasionally be beneficial, but it is not the most effective treatment option for severe hypocapnic CSA [19–21].

Adaptive servo-ventilation (ASV) is an alternative mode of positive pressure ventilation. It is well established in the treatment of CSA related to congestive heart failure (CHF) and has the potential to satisfactorily eliminate CSA/CSR, improve LV function and individual exercise capacity, and can reduce arousals, sleep fragmentation and sympathetic activation [20–26]. ASV is also used to treat hypocapnic CSA of origins other than CHF [19,27] and the similarities of the pathophysiological features of CSA related to CHF, idiopathic CSA and CSA post stroke [7] lead to the suggestion that ASV might also be effective in the treatment of persistent CSA after stroke. Only a few studies have evaluated the effectiveness of ASV and adherence to therapy in patients with non-CHF CSA. Some studies included stroke patients, but they were included within very heterogeneous groups of patients with a multitude of neurological disorders and idiopathic CSA, thus not allowing a more detailed analysis. For this study, we aimed to evaluate the role of ASV in the treatment of persistent CSA in post-acute stroke patients.

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2. Methods

2.1. Setting and procedures

A retrospective single-centre analysis was conducted to evaluate safety and efficacy of ASV for the treatment of persisting CSA in postacute stroke patients. The study was approved by the institutional review board and the Cantonal Ethics Commission Bern (REC No. 04–09-13). The records of all patients treated with ASV between January 2005, when ASV became routinely available at our institution, and December 2012 were reviewed. Patients were included if all of the following applied: (1) history of ischemic stroke >1 month before baseline diagnosis of SDB; (2) non-hypercapnic CSA/CSR with >50% of apneas/hypopneas central in origin, an apnea index (AI) >5/h proven by a polysomnography or cardio-respiratory polygraphy and hypocapnic or normal nightly transcutaneous pCO_2 or arterial daytime pCO_2 in a blood gas analysis; (3) no evidence of CHF, defined by the following characteristics: no history or current symptoms of heart failure, normal current echocardiographic left-ventricular ejection fraction (LVEF) or normal B-type natriuretic peptide (BNP); (4) treatment with ASV for ≥3 months. Patients with acute stroke (<1 month before diagnosis of SDB) were excluded.

Clinical information was obtained from sleep medicine consultations and comprehensive sleep medicine questionnaires that were routinely completed by all patients. The following parameters were evaluated: date of ASV initiation, demographics, sleep study results, medical history, clinical symptoms, adherence data as well as ventilator settings, mask leakage, and residual respiratory events. Subjective daytime sleepiness was assessed using the ESS with EDS defined as an ESS of >10 [28]. SDB and sleep stages were defined and scored according to current American Academy of Sleep Medicine guidelines [29]. In Switzerland, treatment reimbursement by the health insurance is contingent upon a mean use of ≥4 h per night and during 75% of nights. We used this threshold to define adherence to therapy. There was no further formal neurological testing during follow-up, but all patients were independent in their daily activities.

Patients were started on ASV (Autoset CS or CS2; ResMed, Bella Vista, NSW, Australia) as outpatients with the following initial ventilator settings: end-expiratory pressure (EEP) was set at a minimal level of 5 cmH_2O and the variable pressure support was set to a range of 3–9 cmH_2O. The automatic back-up rate of the ventilator was used, which is automatically activated during prolonged apneas and targets 15 breaths/min. EEP and range of pressure support were adjusted manually as necessary to eliminate airway obstruction and stabilize breathing. Adequacy of pressure settings was checked within the first week of treatment. Adjustments to reduce residual respiratory events or increase comfort were made on the basis of the ventilator-reported residual apneas and patients' feedback in the outpatient setting. Patients were then followed up routinely as outpatients every 2–3 months for the first 6 months. At each visit the data on residual respiratory events measured by the ventilator built-in flow sensor and stored on the data chip were downloaded and analyzed with the Reslink® program (ResMed, Bella Vista, NSW, Australia). Thereafter, clinical outcome and quality of ASV treatment were surveyed at least annually according to our institutional and national recommendations. Additional follow-up visits were planned as needed to optimize treatment quality and adherence or if irregularities occurred. The primary outcome parameter was the efficacy of ASV as measured by the reduction of AHI. Secondary endpoints were adherence to treatment, evolution of daytime symptoms, and safety.

2.2. Statistics

Results are expressed as frequencies, median followed by interquartile range in parenthesis or as mean ± SD unless indicated otherwise. Wilcoxon signed rank test was used to compare means. The significance level of all analyses was set to 5%. Data were analyzed using SPSS V15.0 (Chicago, IL, USA).

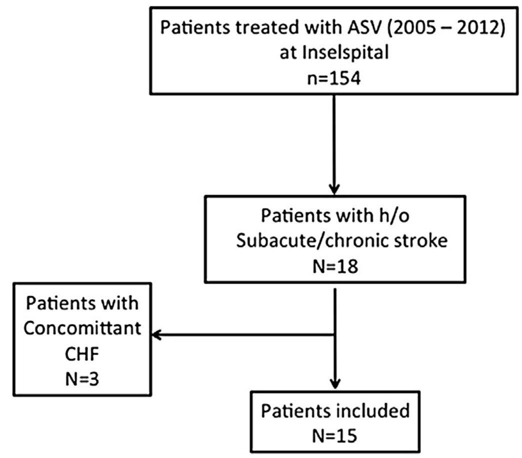

Fig. 1. Flow diagram showing the selection of stroke patients treated with adaptive servo-ventilation (ASV) and inclusion in the study. h/o, history of; CHF, congestive heart failure.

3. Results

3.1. Patients

Fifteen out of 154 patients diagnosed with hypocapnic CSA and treated with ASV were eligible and included in the analysis (see Fig. 1). Patients were predominantly elderly male with a mean ESS at baseline of 8.6 ± 6.4. Baseline characteristics are shown in Table 1. At baseline, all patients had predominately CSA. Stroke distribution included the territory of the middle cerebral artery (7/15 patients) and the posterior cerebral artery (7/15 patients). One patient had multiple infarctions on both vascular territories and hemispheres. There were no strokes in the territory of the anterior cerebral artery. Stroke localizations were equally distributed to both hemispheres and both sides of the cerebellar tentorium. Four

Table 1
Patient baseline characteristics.

No. of patients	15
Anthropometrics	
Age (years)	62 ± 9.4
Body mass index (kg/m^2)	31.3 ± 5.6
Male sex [no. (%)]	13 (87%)
Epworth Sleepiness Scale (ESS)	8.6 ± 6.4
Patients with ESS >10 [no. (%)]	4 (26.7%)
Stroke location [no. (%)]	
Supratentorial	7 (46.7%)
Infratentorial	7 (46.7%)
Mixed	1 (6.6%)
Cardiovascular risk factors [no. (%)]	
Atrial fibrillation	2 (13.3%)
Arterial hypertension	10 (66.7%)
Coronary heart disease	4 (26.7%)
Diabetes mellitus	3 (20%)
Smoking	6 (40%)
Initial treatment before start of ASV [no. (%)]	
CPAP	11 (73.3%)
BIPAP	2 (13.3%)
None	2 (13.3%)
Time interval between stroke and ASV initiation (months)	11 (1; 95)

ASV, adaptive servo-ventilation; CPAP, continuous positive airway pressure; BIPAP, bilevel positive airway pressure; SpO_2, oxygen saturation.
Data are presented as mean ± standard deviation, median followed by interquartile range in parenthesis or number (percentage).

Table 2
Baseline sleep study results.

Respiratory data ($n = 15$)	
Apnea–hypopnea index (events/h recording)	46.7 ± 24.3
Apnea index (events/h recording)	28.5 ± 20.3
Oxygen desaturation index (≥4%) (events/h recording)	33.3 ± 21.8
Mean nocturnal SpO_2 (%)	90.6 ± 3.4
Minimal nocturnal SpO_2 (%)	75.5 ± 11.1
Time spent with SpO_2 <90% (min)	127.5 ± 134.7
EEG data (patients with baseline polysomnography; $n = 10$)	
Total sleep time (min)	349 ± 67
Sleep latency (min)	14 ± 14.6
S1 (%)	30.9 ± 15
S2 (%)	36 ± 21
S3 (%)	9.3 ± 11.3
REM (%)	9.8 ± 6.3
Wake after sleep onset (%)	14 ± 12.6

SpO_2, peripheral capillary oxygen saturation; EEG, electroencephalography; REM, rapid eye movement sleep.
Data are presented as mean ± standard deviation.
Ten patients underwent full attended polysomnography and five patients cardio-respiratory polygraphy.

out of 15 patients had a history of a recurrent ischemic cerebrovascular event. At the time of ASV initiation, all patients were independent in daily life activities and treated as outpatients.

3.2. Sleep study results, prior treatment, ASV adherence and ASV settings/mask leak

All patients had undergone prior polysomnography with transcutaneous pCO_2 measurements ($n = 10$) or cardio-respiratory polygraphy and daytime arterial blood gas analysis ($n = 5$) showing non-hypercapnic central sleep apnea [mean nightly transcutaneous pCO_2, 38 ± 4.7 ($n = 10$); daytime arterial pCO_2, 35.4 ± 2.8 ($n = 5$)]. Baseline sleep study results are shown in Table 2. Most patients were treated initially with CPAP (11 out of 15 patients) or bilevel positive airway pressure (two out of 15 patients) without sufficient reduction of AHI. Two patients were started on ASV without prior other positive airway pressure (PAP) treatment. Data on residual respiratory events were acquired from the ventilator built-in airflow detection system. As shown in Table 3 and Fig. 2, ASV significantly suppressed SDB with a reduction of the mean AHI from 46.7 ± 24.3 to 8.5 ± 12/h ($P = 0.001$) at the first follow-up visit 3 months after initiation of ASV and to 10.7 ± 13.4/h ($P = 0.024$) at the second follow-up visit after 6 months of treatment. AHI remained high in one patient due to a persistent mask leakage that could not be corrected sufficiently because of residual neurological impairment after a severe stroke.

Overall, nightly adherence to therapy was satisfactory. Mean nightly usage was 5 h 20 min ± 2 h 21 min at the first follow-up visit and improved to 6 h 22 min ± 2 h 2 min at the second follow-up visit. In the long term, the mean overall treatment time from initiation of ASV until data collection was 23.3 ± 14.9 months. Two out of 15 patients stopped ASV because of intolerance of the interface, two out of 15 patients died (one recurrent stroke, one car accident), and one patient was lost to follow-up. Ten patients (66.7%) were still on ASV at the time of data collection.

3.3. Impact on daytime symptoms

At baseline, 26% of the stroke patients felt sleepy. Overall ESS score decreased (8.6 ± 6.4 vs 5.6 ± 2.5, $P = 0.08$) at the first follow-up visit for both adherent (>4 h per night) and non-adherent patients, but the difference in ESS score decline did not reach statistical significance. When the threshold to separate adherent from non-adherent patients was lifted to 5 h per night, a dose–response effect to ASV treatment was observed with a significant reduction of ESS (9.0 ± 4.4 vs 4.2 ± 2.0, $P = 0.028$) in the more adherent group of patients (seven patients) (Fig. 3).

3.4. Safety/side-effects

Adaptive servo-ventilation was generally well tolerated and no severe side-effects were reported.

4. Discussion

Our study provides new insights into the use, efficacy, and feasibility of ASV in the treatment of CSA in post-acute ischemic stroke patients. ASV effectively treated CSA, reduced daytime sleepiness in adherent patients, and was well tolerated and safe in the study population.

Though there are good data to support the use of ASV in the treatment of CSA in congestive heart failure [24,30,31], the relevance of persistent CSA related to ischemic stroke, its treatment and the feasibility of its treatment are still less clear. SDB in general is widespread among stroke patients during the acute phase and in the longer term, and it has been shown that OSA and CSA are negative prognostic factors for acute stroke patients. The evidence is growing that persistent OSA in post-acute stroke patients is independently associated with increased mortality and that its treatment with PAP may be beneficial, but the impact of CSA on long-term mortality remains controversial [32]. However, persisting CSA in post-acute stroke shares pathophysiologic features with CSA in CHF, and, in clinical practice and according to current recommendations,

Table 3
Course of therapy.

	Time of diagnosis	Follow-up visit 1 ASV	Follow-up visit 2 ASV
Subjects (no.)	15	15	15
Time interval	–	3 months	6 months
AHI (events/h recording)	54.4 (25; 63.7)	4.7 (0.5; 9.2)[a]	6.6 (1.5; 11.9)[a]
AI	29.6 (12; 45.5)	0.2 (0; 0.6)[a]	0.2 (0; 1.8)[a]
ESS	8.6 ± 6.4	5.9 ± 2.5	6.1 ± 2.7
ASV settings			
EEP	–	5 cmH_2O	5 cmH_2O
Minimum pressure support	–	3 cmH_2O	3 cmH_2O
Maximum pressure support	–	10 cmH_2O (9; 12)	10 cmH_2O (8; 12)
Respiratory back-up rate	–	Automatic	Automatic
Nightly ASV adherence	–	5 h 20 min ± 2 h 21 min	6 h 22 min ± 2 h 2 min

ASV, adaptive servo-ventilation; AHI, apnea–hypopnea index; AI, apnea index; ESS, Epworth Sleepiness Scale; EEP, end-expiratory pressure.
Data are presented as mean ± standard deviation, or median followed by interquartile range in parenthesis if not specified otherwise.
[a] $P < 0.05$ compared with baseline.

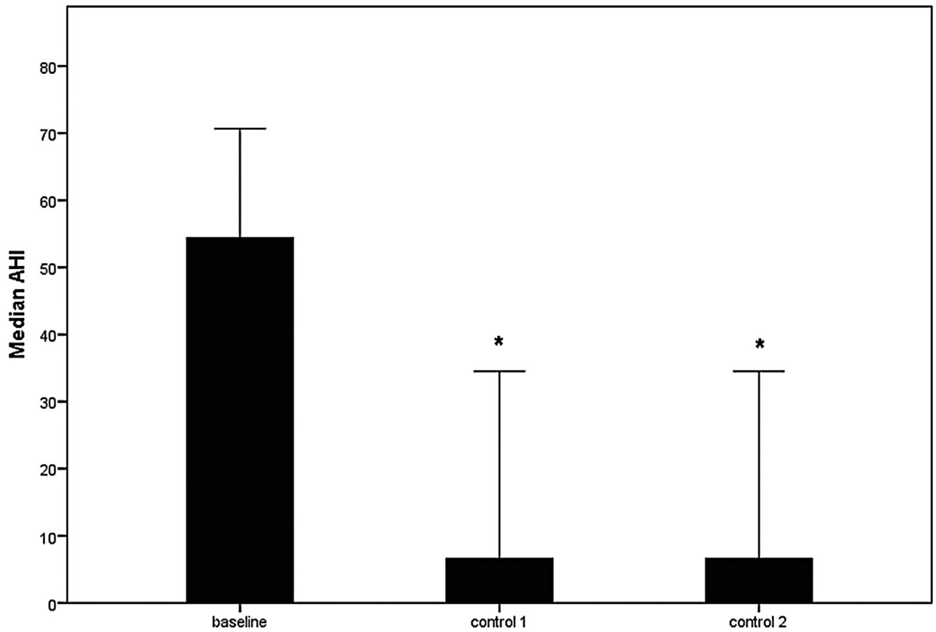

Fig. 2. Sufficient and significant reduction of apnea–hypopnea index (AHI) at follow-up visits 1 and 2 after initiation of adaptive servo-ventilation in 15 patients with central sleep apnea to ischemic stroke. $^*P < 0.05$ compared with baseline.

treatment of persistent severe CSA after stroke can be considered [33]. In our cohort, ASV was feasible, well tolerated, and effective in controlling central respiratory events in patients with postacute ischemic stroke. Interestingly, most of our patients were ineffectively treated with other modalities of PAP treatment, and only the introduction of ASV effectively suppressed CSA, which is comparable with treatment results in CHF patients [19,20] and patients with different neurological disorders [27].

Adherence to PAP therapy is often impaired after stroke secondary to sensomotoric neurologic deficits, such as limb paresis and aphasia [34,35]. Additionally, adherence to therapy may be further

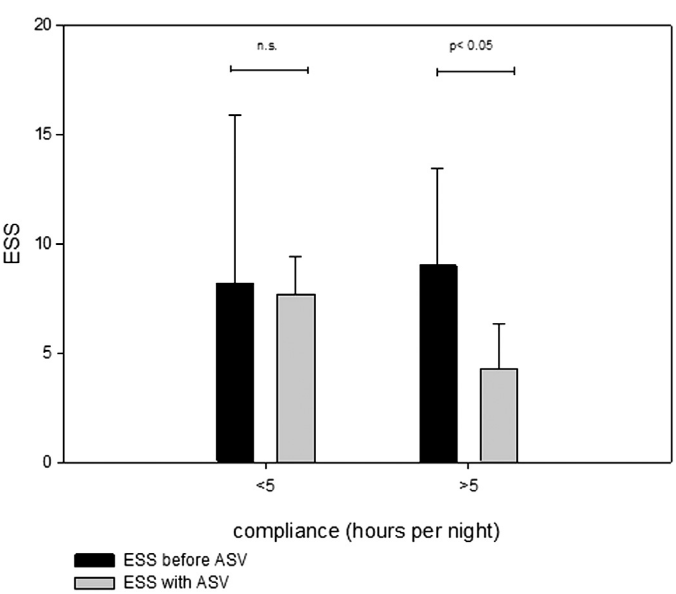

Fig. 3. Change in self-reported daytime sleepiness on the Epworth Sleepiness Scale (ESS) in response to the nightly use of adaptive servo-ventilation. Patients are separated by a threshold of a mean use of 5 h per night. n.s., non-significant.

reduced in patients who are clinically asymptomatic from SDB [35]. In our study, adherence to therapy was surprisingly good at follow-up visits with a mean nocturnal use of >5 h at both visits, despite the absence of relevant EDS at baseline. This is consistent with the findings of Carnevale et al. [27], who described similar treatment compliance in a subgroup of patients treated with ASV for CSA related to etiologies other than CHF, including neurologic diseases and disorders. The good adherence in our cohort might be explained partly by the fact that most patients were already familiar with PAP therapy before starting ASV and that they were all independent in their daily activities after stroke.

Most patients did not feel sleepy at baseline by definition, which is in line with a lower perceived level of sleepiness in stroke patients seen in other studies [1,36]. Nevertheless, patients in our study experienced a decrease in the ESS score in response to ASV treatment and therefore might have perceived a subjective benefit that encouraged them to use the ASV. Since all of our patients were in a clinically stable, chronic post-stroke condition (median time from stroke event was 11 months), the decrease in ESS score was attributable to the observed beneficial effects of ASV on SDB and consequently improved quality of sleep, rather than to the natural evolution of stroke [6,37–42].

There were several limitations to this study. This was a retrospective observational study with all the limitations that come with this design, and although the sample size is comparatively small we present a well-defined cohort of post-acute stroke patients. Neurological characteristics, their evolution, and the recurrence rate of stroke could not be addressed sufficiently due to the retrospective study design and lack of a more detailed formal neurological testing during respiratory follow-up visits in the sleep clinic. Another limitation might be the fact that echocardiographic examinations were not available for all patients to safely rule out occult left ventricular or diastolic dysfunction. However, if no echocardiography was available, BNP within normal values was required. BNP level within normal values has been shown to rule out relevant diastolic left ventricular dysfunction in several patient populations, including patients with atrial fibrillation or heart failure with preserved ejection fraction [43,44]. The limitations of the present study prevent conclusions

from being drawn on the general population. Nevertheless, the data on ASV treatment in CSA in post-acute stroke patients extend prior observations on ASV treatment in indications other than CHF and can be seen as suggestive evidence for the feasibility, efficacy, and safety of ASV for CSA in this population.

Considering the paucity of data on treatment of CSA in stroke, larger randomized trials are warranted to further evaluate and establish the definite role of ASV with regards to the outcome of untreated central sleep apnea on survival, recurrent stroke, brain function, and cognitive impairment.

In conclusion, our data suggest that ASV is a feasible and well-tolerated therapeutic option to treat CSA in post-acute stroke patients with an effective suppression of abnormal respiratory events during sleep and an improvement of ESS scores.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2014.06.013.

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